

WHAT IS CLAIMED IS:

- 5           1. An isolated nucleic acid encoding a polypeptide comprising at least one of the biological activities of OPG wherein the nucleic acid is selected from the group consisting of:
- 10               a) the nucleic acids shown in Figures 2B-2C (SEQ ID NO:120), 9A-9B (SEQ ID NO:122), and 9C-9D (SEQ ID NO:124) or complementary strands thereof;
- 15               b) nucleic acids which hybridize under stringent conditions with the polypeptide-encoding regions as shown in Figures 2B-2C (SEQ ID NO:120), 9A-9B (SEQ ID NO:122) and 9C-9D (SEQ ID NO:124);
- c) nucleic acids which hybridize under stringent conditions with nucleotides 148 through 337 inclusive as shown in Figure 1A; and
- 20               d) nucleic acid which are degenerate to the nucleic acids of (a), (b) and (c).
2. The nucleic acid of Claim 1 which is cDNA, genomic DNA, synthetic DNA or RNA.
- 25           3. A polypeptide encoded by the nucleic acid of Claim 1.
4. The nucleic acid of Claim 1 including one or more codons preferred for Escherichia coli
- 30               expression.
5. The nucleic acid of Claim 1 having a detectable label attached thereto.
- 35           6. The nucleic acid of Claim 1 comprising the polypeptide-encoding region of Figure 2B-2C (SEQ ID

7. The nucleic acid of Claim 6 having the  
5 sequence as shown in Figure 9C-D (SEQ ID NO:124) from  
nucleotides 158-1297.

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12. The host cell of Claim 11 which is selected from the group consisting of CHO, COS, 293, 3T3, CV-1 and BHK cells.

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15. A transgenic mammal comprising the expression vector of Claim 8.

16. The transgenic mammal of Claim 15 which  
35 is a rodent.

18. A process for the production of OPG  
comprising:

19. A purified and isolated polypeptide comprising OPG.

21. The polypeptide of Claim 20 which is human OPG.

23. The polypeptide of Claim 21 having the  
25 amino acid sequence as shown in Figure 2B-2C (SEQ ID  
NO:121), Figure 9A-9B (SEQ ID NO:123), or Figure 9C-9D  
(SEQ ID NO:125) or a derivative thereof.

25. The polypeptide of Claim 23 having the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 32-401 inclusive.

26. The polypeptide of Claim 19 which is characterized by being a product of expression of an exogenous DNA sequence.

5 27. The polypeptide of Claim 26 wherein the DNA is cDNA, genomic DNA or synthetic DNA.

10 28. The polypeptide of Claim 19 which has been modified with a water-soluble polymer.

29. The polypeptide of Claim 28 wherein the water soluble polymer is polyethylene glycol.

15 30. A polypeptide comprising:  
an amino acid sequence of at least about 164 amino acids comprising four cysteine-rich domains characteristic of the cysteine rich domains of tumor necrosis factor receptor extracellular regions; and  
an activity of increasing bone density.

20 31. A polypeptide comprising the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123) or Figure 9C-9D (SEQ ID NO:125) having an amino terminus at residue 22, and  
25 wherein from 1 to 216 amino acids are deleted from the carboxy terminus.

30 32. The polypeptide of Claim 31 comprising the amino acid sequence from residues 22-185, 22-189, 22-194, or 22-201 inclusive.

33. The polypeptide of Claim 32 further comprising an Fc region of human IgG1 extending from the carboxy terminus.

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34. A polypeptide comprising the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123) or Figure 9C-9D (SEQ ID NO:125) having an amino terminus at residue 22, wherein  
5 from 1 to 10 amino acids are deleted from the amino terminus and, optionally, from 1 to 216 amino acids are deleted from the carboxy terminus.

35. The polypeptide of Claim 34 comprising  
10 the amino acid sequence from residues 27-185, 27-189, 27-194, 27-401, or 32-401 inclusive.

36. The polypeptide of Claim 35 further comprising an Fc region of human IgG1 extending from  
15 the carboxy terminus.

37. A polypeptide selected from the group consisting of:

20 huOPG [22-201]-Fc  
huOPG [22-401]-Fc  
huOPG [22-180]-Fc  
huOPG met [22-401]-Fc  
huOPG Fc-met [22-401]  
25 huOPG met [22-185]  
huOPG met [22-189]  
huOPG met [22-194]  
huOPG met [27-185]  
huOPG met [27-189]  
huOPG met [27-194]  
30 huOPG met [32-401]  
huOPG met-lys[22-401]  
huOPG met [22-401]  
huOPG met [22-401]-Fc (P25A)  
huOPG met [22-401] (P25A)  
35 huOPG met [22-401] (P26A)  
huOPG met [22-401] (P26D)

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huOPG met [22-194] (P25A)
huOPG met [22-194] (P26A)
huOPG met met-(lys)3 [22-401]
huOPG met met-arg-gly-ser-(his)6 [22-401]
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38. A nucleic acid encoding the polypeptide of Claim 37.

39. An antibody or fragment thereof which  
10 specifically binds to OPG.

40. The antibody of Claim 39 which is a monoclonal antibody.

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OPG in a biological sample comprising:

incubating the sample with the antibody of Claim 39 under conditions that allow binding of the antibody to OPG; and

20 detecting the bound antibody.

42. A method to assess the ability of a candidate substance to bind to OPG comprising:

incubating OPG with the candidate substance  
25 under conditions that allow binding; and  
measuring the bound substance.

43. A method of regulating the levels of OPG in an animal comprising modifying the animal with a nucleic acid encoding OPG.

44. The method of Claim 43 wherein the nucleic acid promotes an increase in the tissue level of OPG.

46. A pharmaceutical composition comprising a therapeutically effective amount of OPG in a pharmaceutically acceptable carrier, adjuvant, solubilizer, stabilizer and/or anti-oxidant.

48. The composition of Claim 47 wherein the OPG has the amino acid sequence as shown in Figure 9B.

50. The method of Claim 49 wherein the polypeptide is human OPG.

25 52. The method of Claim 51 wherein the bone  
disorder is selected from the group consisting of  
osteoporosis, Paget's disease of bone, hypercalcemia,  
hyperparathyroidism, steroid-induced osteopenia, bone  
loss due to rheumatoid arthritis, bone loss due to  
30 osteomyelitis, osteolytic metastasis, and periodontal  
bone loss.

53. The method of Claim 49 further comprising administering a therapeutically effective amount of a substances selected from the group consisting of bone morphogenic proteins BMP-1 through

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of osteoprotegerin monomers.

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interchain disulfide bonds.

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add B9